Effect of age on susceptibility to post-traumatic infection in the elderly

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Abstract
Previous work has demonstrated an age-related decline in neutrophil function, including a decline in phagocytic capacity, with age in healthy individuals. This decline in function may contribute to increased susceptibility to bacterial infections in the elderly population. The present study has investigated the effects of age on susceptibility to infection and neutrophil function in elderly humans following mild trauma. Specifically, we have measured neutrophil function in 44 patients, all of whom had no significant co-morbidity, were over 65 years old (mean age 82.5 years) and had sustained a fractured neck of femur. We obtained neutrophils and examined the process of microbial engulfment by phagocytosis and the bactericidal mechanism of superoxide production. In the 5-week period after trauma, almost half of the elderly trauma patients succumbed to bacterial or fungal infection, with a predominance of chest and urinary tract infections. When examining neutrophil function, a decline in superoxide production was observed in neutrophils from the elderly trauma group at the time of hip fracture when compared with those from healthy elderly controls, and this was maintained 5 weeks after trauma. This was accompanied by an age-related reduction in phagocytic function during this period. We propose that trauma and an age-related decline in neutrophil function combine to decrease the immune response to bacteria in the elderly.

Introduction
It is now well accepted that aging is associated with a decline in immune function [1,2], termed immune senescence, and that this is likely to contribute significantly to the increase in susceptibility to infection in the elderly [3]. Reduced neutrophil function has been reported by several groups to be likely to play an important role in immune senescence [4–8] and to underlie the increased incidence of bacterial infections in the elderly.

Our present study has examined elderly individuals suffering from a mild trauma, namely fractured neck of femur. These patients are known to be particularly prone to bacterial and fungal infection, suggesting a role for trauma in further compromising immune function in the elderly. Physical injury is known to raise circulating levels of stress hormones, notably corticosterones, which are potent suppressors of immune function [9,10] and would be expected to increase susceptibility to infection following injury. If stress hormones were the main factors affecting immune status following injury, then it would be predicted that young and old people would have similar infection rates following mild trauma, such as a limb fracture. Previous studies examining infection after trauma have shown a high incidence of respiratory tract and urinary tract infections [9,11]. However, these studies do not help to explain the raised infection rates in elderly trauma patients, as they examined a variety of cases of severe multiple trauma, whereas hip fracture is considered to be a mild trauma. In addition, age was not taken into account in these previous studies. Other work has shown age to be an important factor when examining risk of infection after penetrating abdominal trauma [10], while others have shown that age was not an important factor in relation to infection at the wound site [12].

Infections in trauma patients
To test the hypothesis that age is an important factor for determining susceptibility to infection after mild trauma, elderly individuals (>65 years) were recruited to the study having suffered fractured neck of femur. The occurrence of infection was monitored over the 5-week period after trauma. Neutrophil function was assessed immediately after trauma and again 5 weeks after trauma. Neutrophil phagocytic ability and production of superoxide in response to the bacterial peptide fMet-Leu-Phe (fMLP) were assessed. Groups of young trauma patients (<35 years), healthy young volunteers (<35 years) and healthy old volunteers (>65 years) were also examined. The study was approved by the local ethics committee, and all subjects gave informed consent to participation.

During the study period, just under half of the elderly patients suffered bacterial or fungal infection within 5 weeks of sustaining a hip fracture (Figure 1). The young control group, each of whom had suffered a single limb fracture, although much smaller in number (nine patients), did not have any post-trauma infections during the study period. The chest
Post-traumatic infections in elderly trauma patients
All patients in the study were assessed for post-traumatic infection in the 5-week period after hip fracture. The incidence and site of infection is indicated. Infection was assessed by positive culture for infecting organisms.

was the major site of infection in the elderly trauma group, with urinary tract infections also significantly represented. The predominant infecting species was *Staphylococcus aureus*.

Neutrophil function in healthy elderly subjects and trauma patients
We found a significant decline in phagocytosis of *Escherichia coli* by neutrophils from healthy elderly subjects: only two-thirds of neutrophils from these subjects had positive phagocytic ability, compared with almost 100% of those from the healthy young group. There was no age-related decrease in the ability of neutrophils to produce superoxide anion in response to the peptide fMLP. However, when examining superoxide production in neutrophils from elderly patients with fractured neck of femur, a dramatic effect was observed, with a highly significant decrease in the superoxide response to fMLP (*P* < 0.0001). This response to fMLP remained suppressed 5 weeks after hip fracture in these patients (Figure 2). In neutrophils from the young trauma group with a single limb fracture, no such pattern of suppressed superoxide production in response to fMLP was observed. The data thus suggest that the observed dramatic decline in superoxide production in response to the peptide fMLP in the elderly was age-related rather than trauma-related.

In contrast with the observations made with neutrophils from healthy elderly individuals, which displayed a significant reduction in phagocytosis of *E. coli*, neutrophils from the elderly mild trauma patients displayed a slightly enhanced level of phagocytosis immediately after trauma. However, phagocytosis then returned to the age-related low level upon recall 5 weeks after hip fracture. Phagocytosis was not affected by trauma in the young control group.

Discussion
The present data show that, after a very common mild trauma (fractured neck of femur), elderly patients are very susceptible to infection with bacterial agents, an effect not seen in young patients with a similar injury. This would appear to rule out the possibility that the body’s response to injury per se is the primary immunosuppressive factor. Instead, it suggests that aging of the immune system reduces the ability to deal with stress, leading to enhanced immune decline. Our data show that neutrophils pass through a critical window of compromised function in the 5 weeks after trauma. During this time the killing ability of the neutrophils was reduced due to a decline in superoxide production, and the age-related low level of phagocytic function was also present. During this period, elderly individuals were very prone to infection, as indicated by the high level of infection in the elderly cohort studied here. As neutrophils are a primary defence against bacterial infections, their reduced function is likely to be of critical importance to infection susceptibility in the elderly.

Exactly how the body’s response to trauma might differ in young people and the elderly is not known. However, it is well established that the production of adrenocortical hormones, which can regulate immune responses, alters with age. Specifically, the production of corticosterone is maintained, while the levels of dehydroepiandosterone (DHEA) fall dramatically [13]. Levels of circulating DHEA are at their peak in early adulthood (20–25 years) and then decline gradually until, at over 70 years of age, levels are only 10–15% of those seen at age 20 years. While corticosterone has potent immunosuppressive properties, DHEA has been shown to be immune enhancing [14]. Following trauma, levels of corticosterone rise in response to physical stress, while DHEA levels do not alter, producing a corticosterone excess. In the elderly, the relative levels of corticosterone compared with those of DHEA would be further enhanced following trauma, in comparison with those of the healthy young group.
a younger person. We propose that this relative excess of corticosterone will contribute to reduced neutrophil function in the elderly, and would be expected to influence their ability to fight bacterial infections. Our data also suggest that replacement of DHEA could be of benefit in the elderly following trauma. Our ongoing studies are investigating the ability of DHEA to increase superoxide responses in neutrophils, as this aspect of neutrophil function would appear to be affected following trauma.

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References

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